

### REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Initially, Applicant wishes to express its appreciation to the Examiner and her supervisor for their courtesy and assistance provided to the Applicants' representative during the personal interview.

Claims 1, 5 and 13 have been amended to more particularly point out and distinctly claim the composition of this invention, by reciting that the composition is "in a solid dosage form". Support is found at page 5, lines 2-5 of the specification.

New claims 83-85 are added which define the mean particle size of the micronized AS-3201 as being in a range of about 0.5  $\mu\text{m}$  to less than about 20  $\mu\text{m}$ . Support for the lower limit of the claimed range is found in the specification in original claim 4.

New claims 86-88 define the mean particle size of AS-3201 as being in a range of above 1  $\mu\text{m}$  to less than about 20  $\mu\text{m}$ . There is no explicit support in the specification for the lower limit. However, one skilled in the art would clearly recognize that the lower limit of above 1  $\mu\text{m}$  was contemplated by the inventors, from the teachings of the specification. For example, original claim 4 specifies that the lower limit of the mean particle size is 0.5  $\mu\text{m}$  as noted above. Furthermore, Example 1 on page 10 of the specification discloses a mean particle size of 1.5  $\mu\text{m}$ . Accordingly, it is respectfully submitted that a lower limit of "above 1  $\mu\text{m}$ " is implicitly and inherently taught by the specification.

Claims 1-20 and 61-88 are pending after the foregoing amendments.

Claims 1-20 and 61-82 are rejected under 35 USC 103 as being unpatentable over Negoro et al. in view of Muller et al. This ground of rejection is respectfully traversed.

(1) First of all, it should be noted that the present invention is characteristic in a pharmaceutical composition comprising as the active ingredient micronized particles of AS-3201 having a mean particle size of less than about 20  $\mu\text{m}$ , preferably of less than about 10  $\mu\text{m}$ , particularly preferably about 0.5 to about 3  $\mu\text{m}$ , in a specific ratio. It is also characteristic in that the micronized particles of AS-3201 include additives in the specified ratios as defined in claims 5, 13 and others.

In view of the characteristic features, the active ingredient exhibits excellent fast-dissolving properties and thereby the pharmaceutical composition can release the active ingredients rapidly.

(2) The Examiner pointed out that Muller et al., U.S. 5,858,410 discloses that the dissolution rate increases as the particles' surface area increases in accordance with the Noyes-Whitney law. However, Muller et al. teach a particle in the range of 10 to 1,000 nm (in the Office Action, the Examiner erroneously cited as in a range of 10 to 1,0000 nm) (10 to 1,000 nm corresponds to 0.01 to 1  $\mu$ m). Such a nanometer size is too small and is not suitable for the purpose of the present invention as is explained hereinafter.

The invention of Muller et al. is concerned with a pharmaceutical nanosuspension which is mainly for the purpose of intravenous administration and for such a purpose the active ingredient shall be such a small size as "nanometer" size. It should also be noted that the preparation of Muller et al. is a suspension, which is clearly different from the pharmaceutical composition in the solid dosage form of the present invention. To emphasize this distinction, present claims 1, 5 and 13 are amended to require that the composition is "in a solid dosage form".

Although the Examiner pointed out that "Muller et al. disclose a marked increase in saturation solubility and in turn dissolution with the reduction of particle diameter and increases surface area from microns to nanometers "(col. 5, lines 58-60 and col. 7, lines 7-10) and further that "the reference teaches a particle in the range of 10 to 1,0000 nm (correct, 1,000 nm) and 65% dissolution rate within ten minutes" (col. 14, lines 49-55 and figures), it is not directly concerned with the fast dissolution properties mentioned in the present invention.

That is, as is seen from the description of Muller et al., col. 14, lines 37-41 and 49-53, the test was carried out by introduction of the drug particles into a 0.9% NaCl solution saturated with the drug. That is, the particles of the drug were superfluously dissolved in a solution saturated with the drug. This is essentially different from the dissolution test by Paddle method in the present invention wherein it is tested how the active compound is dissolved out from the solid form of the composition.

As is emphasized in Applicant's comments to the last Office Action, in the pharmaceutical composition in the solid dosage form (e.g. tablet) of a hardly soluble active

compound, there is usually a problem of less dissolution of the active compound from the composition (e.g. tablet), and hence, it is more important to improve the solubility of the active AS-3201 used in the present invention in order to prepare a pharmaceutical composition having improved dissolving property. Thus, in view of extremely low solubility of the active compound in the present invention, ingenuity is required in order to increase the solubility of the active compound AS-3201.

(3) Since the Examiner said that "Muller et al. disclose that the dissolution rate increases as the particle surface area increases in accordance with the Noyes-Whitney law", and "as a result of increased dissolution rate increases bioavailability", Applicant would like to point out that it has usually been considered that it is not simple and not predictable to increase solubility of a compound by micronization.

Please refer to "Design and Evaluation of Peroral Pharmaceutical Preparations (in Japanese)", edited by Mitsuru Hashida, Yakugyo Jihosya, February 10, 1995, pp. 81-84, 168-171 (cited in the International Search Report of the original PCT/JP98/04658) thereof (which was submitted as Supplemental Information Disclosure Statement on September 26, 2000). An English translation of this publication is submitted concurrently herewith.

This publication also mentions:

(i) The Noyes-Whitney's equation predicts that the larger the specific surface area of the drug substance, the faster the dissolution rate is obtained." (cf. English translation of pp. 81-84 at page 2, lines 9-8 from the bottom)

(ii) Size reduction by pulverization will increase surface area causing an increase in dissolution rate. In addition, as seen from the Ostwald-Freundlich's equation (Equation 5-8) described in Chapter 5, this results also in an increase in solubility itself. (cf. English translation of pp. 168-171 at page 1, lines 12-14).

(iii) It has been reported about many insoluble drugs, for example, phenytoin<sup>3)</sup>, nitrofurantoin<sup>4)</sup>, benoxaprofen<sup>5)</sup>, and others<sup>6,7)</sup>, that size reduction can improve the bioavailability. (cf. English translation of pp. 168-171 at page 1, lines 18-20)

However, this publication also discloses the following opposite teachings:

(A) However, in practice, pulverization alone can not always elevate the dissolution rate. (cf. English translation of pp. 81-84 at page 3, lines 11-12)

(B) However the size should be of the submicron level or less for a great influence of size reduction to be exerted on solubility<sup>1,2)</sup>, and therefore pulverization usually made on many drugs may not be very effective in increasing the solubility by size reduction. (cf. English translation of pp. 168-171 at page 1, lines 14-17)

(C) However, in some cases, the finer the particle is, the more easily flocculation occurs, causing reduction of the surface area in contact with water (effective surface area), and thus the dissolution rate of some drugs is even decreased by pulverization. In particular, hydrophobic drugs are very apt to flocculate. As shown in Fig 7-2, the dissolution rate of pulverized griseofulvin is slower than that of non-pulverized griseofulvin<sup>9)</sup>. (cf. English translation of pp. 168-171 at page 1, lines 8-3 from the bottom)

(D) Once a pulverization equilibrium has been reached, although the particle size will be kept unchanged on continued pulverization, the mechanical energy applied to particles is consumed for destruction of the crystal structure, and this increases consequently lattice strain and lattice disturbance. This indicates that pulverization not only increases the surface area of particles but also exerts a great influence on the reactivity and stability of the solid; therefore attention should be paid to such mechanochemical changes in the properties when a drug is pulverized. It is often experienced that pulverization makes a drug amorphous. Fig. 7-4 shows that cepalexin, when pulverized by a ball mill, becomes amorphous with decreased degree of crystallinity<sup>12)</sup>. Ampicillin also becomes amorphous on pulverization<sup>13)</sup>. Fostedil<sup>14)</sup> and chloramphenicol palmitate<sup>15)</sup> have been found to show transformation to other crystal forms. In these cases the solubility itself will change. In general, solubility increases when the drug has become amorphous but the stability is lowered in most cases, which should be kept in mind. (cf. English translation of pp. 168-171 at page 2, line 20 to the end of the line)

(E) Mechanochemical effects, such as heat or mechanical pressure generated during pulverization, are problematic in many cases. (cf. English translation of pp. 168-171 at page 5, lines 4-5)

Please also be advised that in the cited Muller et al. reference, even as to saturation solubility, it is mentioned as "an increase in the saturation solubility when the particle size is decreased is postulated in the Ostwald-Freundlich equation..., but this does not have an effect

on particles in the micrometer range..." (cf. Muller et al., col. 5, end of the line - col. 6, line 7)

As is seen from the above, even by decreasing the particle size, it does not necessarily always result in increase of the dissolving rate, and further it is not necessarily predicted whether the drug is well pulverized with keeping the stability of the drug.

Besides, like in griseofulvin, drugs are sometimes flocculated by pulverization, and thereby, the dissolution rate of pulverized product is slower than that of non-pulverized product. Further, some products become amorphous by pulverization, which results in significant lowering of the stability of the drug.

(4) The Examiner further pointed out that Negoro et al. teach the instantly claimed aldose reductase inhibitor compound in a pharmaceutical composition for the treatment of diabetes and also refer to the composition of Example 29.

As is also recognized by the Examiner, Negoro et al. do not specify the particle size of the active compound or the dissolution rate. Negoro et al. does not teach or even suggest to micronize the active compound to the specific range nor the effects of the micronization on the dissolution rate.

In order to prove experimentally that the compound prepared by the method disclosed in Negoro et al. does not show the desired fast dissolution properties of the micronized compound of the present invention, comparative experimental data are submitted in Declaration form. (See attached Rule 132 Declaration of Mr. Mamoru Ohashi)

As is seen from the comparative experiments, the compound AS-3201 is prepared in the manner described in Example 1 of Negoro et al. This compound had a mean particle size of about 87  $\mu\text{m}$ , as described in Experiment 1.(3), as described on page 3 of the Declaration. These particles were used to prepare Tablet C.

The same particles were micronized according to the present invention to a particle size of about 1.5  $\mu\text{m}$ , and 10  $\mu\text{m}$ ,  $\nabla$ 4-mTNF as described in Experiment 1.(1) and (2), respectively. The micronized particles were prepared into Tablet A and Tablet B, respectively.

Tablets A, B and C were then subjected to dissolution according to the Paddle method, and the dissolution rates of AS-3201 were measured from each tablet. The results of these experiments are shown in Figure 1 attached to the Declaration.

Figure 1 shows that the dissolution of AS-3201 from Tablet A containing the particle size of about 1.5  $\mu\text{m}$  was about 90% at 15 minutes and about 100% at 60 minutes.

The dissolution of AS-3201 from Tablet B containing particles of 10  $\mu\text{m}$  was about 65% at 15 minutes and about 80% at 60 minutes.

In comparison, the dissolution of AS-3201 from Tablet C according to Negoro et al. having a particle size of about 87  $\mu\text{m}$  is only about 10% after 15 minutes and only about 15% after 60 minutes.

These experiments demonstrate that the composition according to the claimed invention has an unexpectedly superior fast dissolution rate compared to the composition according to Negoro et al. Such excellent dissolution characteristics of the present invention could never be predicted from Negoro et al., even taking into consideration the teachings of Muller et al.

This excellent dissolution rate is especially unexpected, in view of the low solubility of AS-3201 used in the present invention. The present inventors have studied the means for micronizing AS-3201 crystals suitable for preparing the desired pharmaceutical composition and have found that, when the AS-3201 crystals are micronized in a specific particle size, i.e. in a mean particle size of less than 20  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$ , AS-3201 can exhibit excellent solubility. As a result, the present inventors succeeded in preparation of an AS-3201 containing pharmaceutical composition which has extremely improved dissolving properties and superior bioavailability in comparison with a composition prepared by using non-micronized AS-3201 crystals according to Negoro et al., as is clear from comparison of the products of Examples and Reference Examples of the specification and attached Declaration.

II: Re: Rejection of claims 61-62 under 35 USC 103(a) as being unpatentable over Negoro et al. (5,258,382) in view of Muller et al. (5,858,410) in further view of Schneider et al. (5,356,636)

As is explained above, neither Negoro et al. nor Muller et al. teach or even suggest the specific pharmaceutical composition of the present invention.

The Examiner further pointed out as "Muller et al. teach the use of stabilizers to cover the surface of the particles to prevent aggregation (col. 7), further as to another secondary reference, as "Schneider et al. teach the instant acids as stabilizer (col. 4, lines 68) in composition", and then further as "it would have been obvious to one of ordinary skill in the art at the time the invention was made to add the instant acids since Schneider et al. teach these acids as stabilizers for the actives."

Firstly, although in Muller et al., dispersion-stabilizing substances and charge stabilizers are also incorporated in order to prevent aggregation of the particles as shown in claims 12-15 and claims 16-18, which are effective for prevention of aggregation of particles in the suspension. These substances used in Muller et al. are essentially different from the stabilizer (i.e. acidic substance such as citric acid, tartaric acid, maleic acid, malic acid) of the present invention in both kinds and in the object and effect of use thereof.

Secondly, the invention of Schneider et al. is concerned with stable dry powders which are insoluble in hot water (and in which one or more fat-soluble vitamins and/or one or more carotenoids are embedded in a gelatin-based matrix), and in case of active substances which are sensitive to oxidation, an antioxidant (e.g. ethoxyquin, BHT, BHA or tocopherol) and a stabilizer (e.g. citric acid, phosphoric acid or phytic acids or salts thereof, etc.) are added. Thus, in Schneider et al., the stabilizer is added merely for the purpose of prevention of oxidation of the active compound. Besides, in working examples in Schneider et al. only phytic acid is used.

On the other hand, in the present invention, the specific acidic substance has an acidity more potent than that of AS-3201 and is incorporated for the purpose of prevention of hydrolysis of the active substance due to the moisture absorption during storage, which is clearly distinguished from the cited Schneider et al.

Accordingly, the present invention as claimed in claims 61 and 62 is never taught or even suggested by those cited references.

In view of the foregoing, it is respectfully submitted that the claims as amended are nonobvious and patentable over the prior art.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Accordingly, reconsideration and allowance is respectfully solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Confirmation No. 9675  
Mamoru OHASHI et al. : Docket No. 2000\_0486A  
Serial No. 09/529,715 : Group Art Unit 1616  
Filed April 19, 2000 : Examiner S. Gollamudi

FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

RESPONSE UNDER 37. CFR 1.111  
EXPEDITED PROCEDURE  
EXAMINING GROUP 1616

AMENDMENT AFTER FINAL

Assistant Commissioner for Patents,  
Washington, D.C.

Sir:

Responsive to the Official Action dated March 26, 2002, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend the claims as follows:

1. (<sup>Thrice</sup>~~Twice~~ Amended) A fast-dissolving pharmaceutical composition comprising <sup>in a solid dosage form,</sup> micronized (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone (hereinafter referred to as "AS-3201") having a mean particle size of less than about 20  $\mu$ m in a ratio of about 0.5% by weight to about 25% by weight of the total weight of the pharmaceutical composition,

wherein when a dissolution percentage of AS-3201 from the composition is measured according to the Paddle method, 50% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method.

*Thrice*

*in a solid dosage form*

5. (~~Twice~~ Amended) A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of about 0.5% by weight - 5% by weight, a diluent in a ratio of about 51% by weight - about 93.8% by weight, a disintegrator in a ratio of about 5% by weight - about 35% by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2% by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein when a dissolution percentage of AS-3201 from the composition is measured according to the Paddle method, 50% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method.

*Thrice*

*in a solid dosage form*

13. (~~Twice~~ Amended) A fast-dissolving pharmaceutical composition, which comprises micronized AS-3201 in a ratio of more than 5% by weight and less than about 25% by weight, a diluent in a ratio of about 16% by weight - about 84.3% by weight, a disintegrator in a ratio of about 10% by weight - about 50 % by weight, a binder in a ratio of about 0.5% by weight - about 5% by weight, and a lubricant in a ratio of about 0.2 % by weight - about 4% by weight, relative to the total weight of the pharmaceutical composition,

wherein when a dissolution percentage of AS-3201 from the composition is measured according to the Paddle method, 50% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method.

63. (Amended) The fast-dissolving pharmaceutical composition according to claim 1, wherein 80% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method.

64. (Amended) The fast-dissolving pharmaceutical composition according to claim 2, wherein 80% or more of the AS-3201 in the composition is dissolved within 15 minutes from the start of the method.